

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/00648

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :Please See Extra Sheet.

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 546/288, 289, 291, 300 ; 514/183, 222.2, 228.8, 588, 595, 597, 598; 564/49, 50, 52,

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

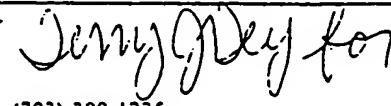
CAS ONLINE, REGISTRY, HCAPLUS

search terms : cancer, raf kinase

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| Y | WO 98/52558 A1 (BAYER CORPORATION) 26 November 1998, (26.11.98) especially Tables 1-4, pages 65-76. | 1-67 |
| Y | WO 98/52559 A1 (BAYER CORPORATION) 26 November 1998 (26.11.98), especially Tables 1-4, pages 15-17. | 1-67 |
| Y,P | Database HCAPLUS, DN 131:87909, DUMAS et al. 'Inhibition of P38 kinase activity using substituted heterocyclic ureas.' Abstract, WO 99/32111, 01 July 1999, see entire document. | 1-67 |
| Y,P | Database HCAPLUS, DN 131:73649, DUMAS et al. 'Preparation of pyrazolyl aryl ureas and related compounds as P38 kinase inhibitors.' Abstract, WO 99/32110, 01 July 1999, see entire document. | 1-67 |

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|-------------------------------------|--|--------------------------|--|
| <input checked="" type="checkbox"/> | Further documents are listed in the continuation of Box C. | <input type="checkbox"/> | See patent family annex. |
| • | Special categories of cited documents: | | |
| "A" | document defining the general state of the art which is not considered to be of particular relevance | "T" | later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| "E" | earlier document published on or after the international filing date | "X" | document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| "L" | document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | "Y" | document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| "O" | document referring to an oral disclosure, use, exhibition or other means | "&" | document member of the same parent family |
| "P" | document published prior to the international filing date but later than the priority date claimed | | |

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|---|--|
| Date of the actual completion of the international search | Date of mailing of the international search report |
| 22 MAY 2000 | 29 JUN 2000 |
| Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 | Authorized officer RITA DESAI Telephone No. (703) 308-1235 |
| Facsimile No. (703) 305-3230 |  |

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| C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT | | |
|---|---|-----------------------|
| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| X | Database HCAPLUS, DN 127:293717, KURIK M.V. et al. 'Optical properties of segmented oligourethane with azomethine terminal fragments.' Abstract, Vysokomol. Soedin. 1996, Vol. 38, No. 12, pages 2038-2041, especially RN# 197149-54-5. | 1-48,60 and 61 |
| X | Database HCAPLUS, DN 127:34137, KUBO et al. 'Preparation of quinoline and quinazoline derivatives inhibiting platelet-derived growth factor receptor autophosphorylation.' Abstract, WO 97/17329. 15 May 1997, see entire document, especially RN # 190726-87-5, 190726-88-6, 190727-39-0, 190727-43-6. | 1-67 |
| X | Database HCAPLUS, DN 126:166148, WINKLER et al. 'Inhibitors of coenzyme A-independent transacylase induce apoptosis in human HL-60 cells.' Journal of Pharmacol. 1996, Vol. 279, No. 2, pages 956-966, see entire document, especially RN# 162793-63-7 and 187173-03-1. | 1-67 |
| X | Database HCAPLUS, DN 98:78152, CHUGAI PHARMACEUTICAL CO. LTD., JAPAN. 'Antitumor benzophenone derivatives.' Abstract, JP 57185219. 15 November 1982, see entire document, especially RN# 3086-71-4. | 1-67 |
| A | Database HCAPLUS, DN 72:79046, HIRT et al. 'Tuberculostatic and cancerstatic polybasic ureas.' Abstract, CH 479557. 15 October 1969, see entire document, especially RN# 5262-16-8. | 1-67 |
| X,P | Database HCAPLUS, DN 131:58658, MILLER et al. 'Inhibition of raf kinase using symmetrical and unsymmetrical substituted diphenyl ureas.' Abstract, WO 99/32436. 01 July 1999, see entire document, especially RN# 228399-32-4. | 1-67 |
| X | Database HCAPLUS, DN 127:273945, DEARDEN et al. 'Quantitative structure-biodegradability studies: an investigation of the MITI aromatic compound database.' Nato ASI Srv. 1996, Vol. 23, pages 93-104, see entire document, especially RN# 24019-05-4. | 1-48, 50 and 61 |
| X | Database HCAPLUS, DN 125:245169, BONWICK et al. 'Production of murine monoclonal antibodies against sulcofuron and flucofuran by in-vitro immunization.' Journal of Immunological Methods. 1996, Vol. 196, No. 2, pages 163-173. See entire document, especially RN# 24019-05-04. | 1-67 |

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest



The additional search fees were accompanied by the applicant's protest.



No protest accompanied the payment of additional search fees.

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International application No.
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A. CLASSIFICATION OF SUBJECT MATTER: IPC (7):

C07D 211/78, 211/72; A61K 31/33, 31/54, 31/535, 31/17; C07C 275/20, 275/22, 275/24, 275/28

A. CLASSIFICATION OF SUBJECT MATTER: US CL :

546/288, 289, 291, 300 ; 514/183, 222.2, 228.8, 588, 595, 597, 598; 564/49, 50, 52,

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claims 1-37,50-58 and 60-67 in part , drawn to compounds pharmaceutical compositions and method of using these, wherein D is -NH-C(O)-NH-, B is a 3-tert butylphenyl or 5 tert butyl or trifluoromethyl (methoxy and / or chloro substituted) phenyl, and R is a non-hetero biaryl linked via an Oxygen atom.

Group II, claims 1-37, 50-58, 60-67 in part , drawn to compounds compositions and methods of using these, wherein D is -NH-C(O)-NH-, B is a 3-tert butylphenyl or a 5 tert butyl or trifluoromethyl (methoxy and/or chloro substituted) phenyl, and R is a biaryl, in which one of them is a pyridine group linked via an Oxygen atom.

Group III, claims 1-37 50-58, 60-67 in part , drawn to compounds pharmaceutical compositions and methods of using these, wherein D is -NH-C(O)-NH-, B is a 3-tert butylphenyl or a 5 tert butyl or trifluoromethyl (methoxy and / or chloro substituted) phenyl , and R is a biaryl, in which one of them is a pyrimidyl linked via an Oxygen atom.

Group IV , claims 1-37, 50-58,60-67 in part , drawn to compounds , pharmaceutical compositions and method of using these, wherein D is -NH-C(O)-NH-, B is a 3-tert butylphenyl or a 5 tert butyl or trifluoromethyl (methoxy and / or chloro substituted) phenyl, and R is another hetero group linked via an Oxygen atom (may be subject to further restriction).

Group V, claims 1-37, 50-58,60-67 in part , drawn to compounds , pharmaceutical compositions and a method of using these wherein R is a biaryl or an hetero group linked via an Nitrogen/amide/urea linkage and which may be subject to further restriction depending on the selected hetero group.

Group VI , claims 39, 42,43,45,47,49,59 in part , drawn to a different scope of compounds and compositions , subject to further restriction.

Group VII. claims 38,40,41,44,46,48,49,50 in part , drawn to a different scope of compounds of formula I , subject to further restriction.

Group VIII, claims 50-54 , drawn to various salts of compounds and their compositions , may be subject to further restriction.

They form an improper Markush Grouping and do not have a common core.

I. The inventions listed as Groups I, II, and III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

(f) "Markush Practice." The situation involving the so-called "Markush practice" wherein a single claim defines alternatives (chemical or non-chemical) is also governed by Rule 13.2. In this special situation, the requirement of a technical interrelationship and the same or corresponding special technical features as defined in Rule 13.2, shall be considered to be met when the alternatives are of a similar nature.

(i) When the Markush grouping is for alternatives of chemical compounds, they shall be regarded as being of a similar nature where the following criteria are fulfilled:

(A) all alternatives have a common property or activity, and

(B)(1) a common structure is present, i.e. a significant structural element is shared by all of the alternatives, or

(B)(2) in cases where the common structure cannot be the unifying criteria, all alternatives belong to a recognized class of chemical compounds in the art to which the invention pertains.

(ii) In paragraph (f)(i)(B)(1), above , the words "significant structural element is shared by all of the alternatives" refer to cases where the compounds share a common chemical structure which occupies a large portion of their structures, or in case the compounds have in common only a small portion of their structures, the commonly shared structure constitutes a structurally distinctive portion in view of the existing prior art. The structural element may be a single component or a combination of individual components linked together.

The different A and D along with the L's, R's and M substituents have so many variables with the heterocyclic and non-hetero groupings . they have different bonding and properties . and have achieved a different status in the art . and

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is burdensome to search and hence are objected to as being drawn to an improper Markush group on the grounds of lack of a common nucleus. The terms A, B,L's, R's and M are so broad in scope that a prior art reference anticipating the claims with respect to one member under 35 USC 102(b) would not render obvious the same claims under 35 USC 103a with respect to another member. The improper Markush group rejection finds basis in case law, compare *In re Swenson* 56 USPQ 180; *In re Ruzicka*, 66 USPQ 226; *In re Winnek*, 73 USPQ 225; *In re Harnisch*, 206 USPQ 300, 305 (CCPA 1980). In view of the foregoing, restriction is required.